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GRISEOFULVIN *

Great interest has greeted the new antifungal agent, griseofulvin (Fulvicin-Schering; Grifulvin-McNeil), developed by Glaxo Laboratories in England. This material was isolated and then forgotten for nearly twenty years. It is obtained from various species of Penicillium, namely, P. griseofulvin, P. janczewski, and P. patulum. Unlike penicillin, it is not bactericidal; furthermore, it differs immunologically from penicillin, and has been given to patients known to be sensitive to penicillin without reaction. Griseofulvin now makes possible successful systemic treatment of many superficial fungous infections (H. Blank and F. J. Roth, A.M.A. Arch. of Derm., 79:259, 1959). Excellent response is obtained in ringworm of the scalp and of the smooth skin caused by common species of dermatophytes. Chronic nail deformities caused by filamentous fungi have also shown satisfactory response, even in cases of many years' duration.

SENSITIVITY - In vitro studies indicate that common superficial fungi, including Microsporum canis, M. gypseum, M. audouini, Epidermophyton floccosum, Trichophyton tonsurans, T. mentagrophytes, T. megnini, T. gallinae and T. rubrum are inhibited by very low concentrations of griseofulvin. The effect is fungistatic rather than fungicidal. The development of resistance to the drug clinically has not yet been encountered. The following fungi were found to be insensitive to griseofulvin: Candida albicans, Cryptococcus neoformans, Sporotrichum schenckii, Hormodendrum compactum, Phialophora verrucosa, Blastomyces dermatitidis, B. brasiliensis, Histoplasma capsulatum, Coccidioides immitis, and Mucor and Aspergillis species. There is some evidence that secondary infection with Candida albicans may result from griseofulvin therapy, especially when the lesions being treated are in folds of the skin.

DOSAGE - Although dosage schedules are still under study, the dosage is usually 250 mgs. three or four times a day in adults, with half the adult dose for children. Larger doses may prove to be necessary in some instances. The duration of therapy may vary from three to four weeks in tinea capitis to four to six months or longer in infections of the nails with filamentous fungi. Topical application is effective, but less so than oral dosage.

A good deal is known about acute toxicity from both animal experiments and clinical experience. In rats, with intravenous and intraperitoneal injections of huge doses (in the range of 200 mg./kg.), G.E. Paget and A. L. Walpole (Nature,

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182: 1320, 1958) found interference with mitosis and spermatogenesis. In our Laboratory of Mycology, with doses comparable to those in man, Schwarz found no toxic effects in animals or changes in fertility rates. In man, sperm count and testicular biopsies have been reported as without change; nevertheless, it is too early to dismiss the possibility of damage, at least from long-term therapy.

SIDE EFFECTS - Side reactions in humans have included gastrointestinal disturbances, usually mild, occasional flares of old colitis, transitory leukopenia, drug rashes of mild to moderate degree, and such vague reactions as headaches, fatigue, insomnia, etc. Despite the apparent absence of serious side effects, our knowledge of chronic toxicity and chronic side effects is inadequate. Although no chronic effects have yet been reported with the drug used continually for 8 to 12 months for onychomycosis, the safest course at present for the general practitioner is to postpone long-term therapy or repeated courses of treatment until enough time has elapsed to permit evaluation of chronic toxicity.

The possible development of resistant strains of dermatophytes, the frequency of recurrence of infections after therapy is discontinued, as well as the possibility of chronic toxic and allergic reactions, are among the questions about griseofulvin therapy still to be answered by long experience with the drug. In view of such questions, it will be particularly unfortunate if this intriguing agent is used for mild fungous disease involving restricted areas amenable to local treatment with other drugs, or for infections with fungi known to be resistant to the action of the drug, for example, infections with Candida albicans. The availability of griseofulvin does not lessen the need for careful differential diagnosis, and in many cases, for fungous culture tests. Griseofulvin is available in 250-mg. tablets at a cost of about 25 to 35 cents per tablet.

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CARBONIC ANHYDRASE INHIBITORS

Although the carbonic-anhydrase-inhibiting drugs were originally developed as diuretics, their major usefulness is now in the treatment of glaucoma. These drugs include: acetazolamide (Diamox-Lederle), ethoxzolamide (Cardrase-Upjohn), dichlorphenamide (Daranide-Merck) and methazolamide (Neptazane-Lederle). As oral diuretics, they have been largely replaced by chlorothiazide (Diuril-Merck) and hydrochlorothiazide (Hydrodiuril-Merck; Esidrix-Ciba); nevertheless, they retain a definite usefulness in certain conditions.

USE AS DIURETICS - The diuretic effect of these drugs results from their inhibition of the enzyme, carbonic anhydrase, in the renal tubules. This action reduces the tubular reabsorption of bicarbonate, resulting in greater excretion of sodium than of chloride. The effect is self-limited, however, since the consequent metabolic acidosis prevents further diuretic action by the carbonic anhydrase inhibitor. (The reduced bicarbonate content of the glomerular filtrate can be completely reabsorbed in the tubules without the aid of carbonic anhydrase.) As diuretics, the drugs are most effective in the congestive failure of cor pulmonale accompanied by respiratory acidosis. The use of Diamox was followed

by symptomatic and clinical improvement in about half of a series of 17 such cases (W. B. Schwartz, et al., Ann. Int. Med., 42: 79, 1955); good diuresis was correlated with the high serum bicarbonate usually present in pulmonary heart failure. In other types of severe congestive failure, the carbonic anhydrase inhibitors have shown little if any diuretic effect (R. W. Berliner and J. Orloff, Pharmacological Revs., 8: 137, 1956). When used simultaneously with parenteral mercurials, they may actually suppress diuresis (J. H. Laragh, Postgraduate Med., 25: 528, 1959). In milder, ambulatory congestive failure they may prove effective in small doses (H. Gold, et al., JAMA, 167: 814, 1958). They have also been effective in premenstrual and pregnancy edema.

While these drugs compare favorably with oral mercurials and the xanthines in the management of mild to moderate edema, they are much less effective than chlorothiazide or hydrochlorothiazide. They are useful chiefly in cor pulmonale, and when sensitization or other toxic or side effects prevent the use of more potent diuretics. When these drugs are used as diuretics, intermittent dosage is advisable. In the recommended doses of 250 to 500 mg. daily for Diamox, and equivalent doses for the other drugs (roughly half as much for Cardrase, one-fifth for Daranide), refractoriness usually develops in 48 to 72 hours. An interval of two days after each two days of dosage is suggested by Laragh. Others suggest dosage on alternate days or on three consecutive days each week.

USE IN GLAUCOMA - Since inhibition of carbonic anhydrase activity in the ciliary body of the eye markedly reduces the secretion of aqueous humor, the oral or parenteral administration of a carbonic anhydrase inhibitor sharply decreases intraocular pressure in most patients with glaucoma. The results in acute congestive (narrow angle) glaucoma and secondary glaucoma are especially noteworthy. Systemic acidosis does not inhibit activity of the drugs in the eye, therefore dosage need not be intermittent. The combination of these drugs with miotics, administered around the clock, has been reported to give good control of pressure in chronic, simple glaucoma even when miotics alone are ineffective. In the chronic narrow-angle glaucomas, however, though these drugs may normalize intraocular pressure, they do not prevent the formation of new synechiae and an eventual rise in intraocular pressure; therefore their use is contraindicated except in preparation for an operation. In the treatment of glaucoma, Cardrase was found effective with doses one-half those of Diamox (A. Posner, Am. J. Ophthal., 45: 225, 1958). Daranide is effective in doses one-third to one-fifth those of Diamox. Dosage must, however, be controlled by determination of intraocular pressure.

Equivalent doses of Diamox, Cardrase and Daranide apparently have about the same incidence of side effects, though individual reactions to the three drugs will differ. Diamox has had the longest use, and as a sulfonamide derivative, it has shown the reactions encountered with this class of drugs. Thrombocytopenia, fever, erythema, hives, renal colic, and one case of agranulocytosis have been reported. The milder and more common side reactions, probably related to acidosis and central-nervous-system effects, include burning and other abnormal sensations around the mouth and in the extremities, drowsiness, fatigue, loss of appetite and irritability. A patient who cannot tolerate one of these drugs may be able to tolerate another.

The newest of the carbonic anhydrase inhibitors, Neptazane, may prove to have special usefulness in glaucoma and also in epilepsy. It is able to penetrate the aqueous humor and the cerebrospinal fluid much better than the other drugs; it can produce a large change in intraocular pressure with relatively little effect in the kidney and little systemic acidosis (B. Becker, Am. J. Ophthal., 47: 342, 1959; Jan. supplement); 100 mg. every 8 hours has an effect on the eye equal to that of 250 mg. of Diamox every 6 hours. Carbonic anhydrase inhibitors have proved effective in some cases of petit mal refractory to other anticonvulsants. It has been suggested that the mechanism of action in these cases is the inhibition of carbonic anhydrase activity in brain tissue, perhaps augmented by the induction of a mild metabolic acidosis.

A NEW ANTIHYPERTENSIVE DRUG

Medical Letter consultants in England are enthusiastic about the therapeutic possibilities of a new kind of antihypertensive drug which was recently synthesized and is now undergoing clinical tests in that country. The first published report on the drug has already appeared (A. L. A. Baura, et al., Lancet, 2: 17, 1959). The drug is Darenthin (Burroughs-Welcome), a benzyl quaternary ammonium compound.

In animals, Darenthin has been shown to accumulate selectively in adrenergic nerves, and to block transmission in these nerves. It is not, however, a ganglion-blocking or adrenergic-blocking agent of the familiar kind; it does not interfere with the action of epinephrine or of norepinephrine after these substances have been released at nerve endings or by the suprarenal medulla, or after they have been injected. Like sympathectomy, the drug actually increases sensitivity to epinephrine and norepinephrine; it can therefore cause dangerous elevations of blood pressure in patients whose hypertension is due to pheochromocytoma.

In the initial clinical trials, Darenthin was taken orally by severely hypertensive patients for periods up to eight months. It was found to lower the supine blood pressure and induce a marked postural fall in almost all of the patients. Except for excessive drop in blood pressure, the only side effect definitely attributable to the drug in 36 cases was very slight nasal congestion. The unpleasant and frequently disabling effects caused by the parasympathetic action of the ganglionic blocking agents (constipation, dry mouth and blurred vision) were not observed in the initial trial. Not every severe case was adequately controlled, however; in some cases, chlorothiazide or reserpine seemed to potentiate the hypotensive effect of the drug.

Although Darenthin will not be marketed for some time, The Medical Letter reports briefly on it because it is an original and potentially important therapeutic development. Naturally much more experience is necessary before the initial observations can be confirmed or denied. If continued clinical experience shows that this drug or related compounds fulfill the initial promise in effectiveness and absence of side effects, physicians will have a much needed new agent for the management of severe hypertension.

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